

# CARDIOVASCULAR MEDICINE

## Prognostic value of dobutamine stress echocardiography in patients with previous coronary revascularisation

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**Objective:** To assess the prognostic value of dobutamine stress echocardiography (DSE) in patients with previous myocardial revascularisation.

**Design:** Prospective study.

**Setting:** Tertiary referral centre in Rotterdam, the Netherlands.

**Patients:** 332 consecutive patients with previous percutaneous or surgical coronary revascularisation underwent DSE. Follow up was successful for 331 (99.7%) patients. Thirty eight patients who underwent early revascularisation ( $\leq 3$  months) after the test were excluded from analysis.

**Main outcome measures:** Cox proportional hazards regression models were used to identify independent predictors of the composite of cardiac events (cardiac death, non-fatal myocardial infarction, and late revascularisation).

**Results:** During a mean (SD) of 24 (20) months, 37 (13%) patients died and 89 (30%) had at least one cardiac event (21 (7%) cardiac deaths, 11 (4%) non-fatal myocardial infarctions, and 68 (23%) late revascularisations). In multivariate analysis of clinical data, independent predictors of late cardiac events were hypertension (hazard ratio (HR) 1.7, 95% confidence interval (CI) 1.1 to 2.6) and congestive heart failure (HR 2.1, 95% CI 1.3 to 3.2). Reversible wall motion abnormalities (ischaemia) on DSE were incrementally predictive of cardiac events (HR 2.1, 95% CI 1.3 to 3.2).

**Conclusions:** Myocardial ischaemia during DSE is independently predictive of cardiac events among patients with previous myocardial revascularisation, after controlling for clinical data.

Over the past decade, advances in the invasive management of patients with chronic coronary artery disease have evolved dramatically. Thus, patients with previous coronary interventions constitute a growing subgroup of patients referred for non-invasive testing to evaluate symptoms or to rule out coronary stenosis, graft occlusion, or progression of coronary artery disease. However, the clinical utility of stress testing in the setting of prior surgical or percutaneous coronary intervention has been questioned.<sup>1–3</sup>

Dobutamine stress echocardiography (DSE) has been established as a safe, feasible, and accurate technique for the detection of myocardial ischaemia and assessment of prognosis for patients with known or suspected coronary artery disease, particularly for patients who are unable to perform an adequate exercise stress test.<sup>4–6</sup> However, the prognostic value of DSE for patients with previous coronary revascularisation has not been established. Accordingly, the aim of this study was to assess whether DSE has additive prognostic value relative to clinical variables among patients with previous coronary revascularisation.

### METHODS

#### Patient population

The study population consisted of 332 consecutive patients with previous coronary revascularisation. Patients were unable to perform an exercise test because of orthopaedic limitations, peripheral arterial or neurological diseases, respiratory insufficiency, or deconditioning and they underwent DSE in our centre. If patients underwent DSE more than once after revascularisation, only the results of the first test were included in the study. All patients were enrolled in an electronic registry that accumulated in the course of daily

clinical care. Informed consent was given before testing. The hospital ethics committee approved the protocol.

#### Clinical data

Before the dobutamine stress test, a structured interview and clinical history, including assessment of cardiac risk factors, were obtained. Congestive heart failure was assessed as any current or previous signs or symptoms of breathlessness, abnormal fluid retention, or both. Hypertension was defined as a blood pressure of  $\geq 140/90$  mm Hg or treatment with antihypertensive medication. Diabetes mellitus was defined as a fasting glucose concentration of  $\geq 140$  mg/dl ( $\geq 7.8$  mmol/l) or the need for insulin or oral hypoglycaemic agents. Hypercholesterolaemia was defined as total cholesterol concentration of  $\geq 200$  mg/dl ( $\geq 5.2$  mmol/l) or treatment with lipid lowering medication.

#### Dobutamine stress protocol

Dobutamine stress testing was performed according to a standard protocol as previously reported.<sup>6</sup> Dobutamine was administered intravenously, starting at a dose of 10  $\mu$ g/kg/min for three minutes (5  $\mu$ g/kg/min for patients with resting left ventricular dysfunction). Incremental dobutamine doses of 10  $\mu$ g/kg/min were given at three minute intervals up to a maximum dose of 40  $\mu$ g/kg/min. If the test end point was not reached at a dobutamine dose of 40  $\mu$ g/kg/min, atropine (up to 2 mg) was given intravenously. Blood pressure, heart rate, and ECG were constantly monitored. Test end points were achievement of the target heart rate (85% of maximum age and sex predicted heart rate), horizontal or downsloping ST segment depression  $> 2$  mm at an interval of 80 ms after the J point compared with baseline, severe angina, a

systolic blood pressure fall  $> 40$  mm Hg, blood pressure  $> 240/120$  mm Hg, or significant cardiac arrhythmia. An intravenous  $\beta$  blocker was available to reverse the adverse effects of dobutamine or atropine.

### Stress echocardiography

Two dimensional echocardiographic images were acquired at rest, during dobutamine stress, and during recovery. The echocardiograms were recorded in a quad screen format. Two experienced observers scored the echocardiograms according to a standard 16 segment model as recommended by the American Society of Echocardiography.<sup>7</sup> Regional wall motion and systolic wall thickening were scored on a five point scale (1, normal; 2, mild hypokinesia; 3, severe hypokinesia; 4, akinesia; 5, dyskinesia). Ischaemia was defined as new or worsened wall motion abnormalities during stress, indicated by an increase of wall motion score  $\geq 1$  grade(s) in  $\geq 1$  segment(s). Ischaemia was not considered to be present when akinetic segments at rest became dyskinetic during stress. For each patient, a wall motion score index was calculated at rest and at peak dobutamine stress by dividing the sum of segments scored by the total number of interpreted segments.

### Follow up

Follow up data were obtained in 2003. The mean (SD) follow up period was 24 (20) months. The current status was determined by contacting the patient's general practitioner and by reviewing hospital records. The date of the last review or consultation was used to calculate the follow up time. An outcome event was the composite of cardiac death, non-fatal myocardial infarction, and late ( $> 3$  months) coronary revascularisation. Cardiac death was defined as death caused by acute myocardial infarction, significant cardiac arrhythmias, or refractory congestive heart failure. Sudden death occurring without another explanation was regarded as cardiac death. Non-fatal myocardial infarction was defined according to the guidelines of the joint European Society of Cardiology/American College of Cardiology committee.<sup>8</sup>

### Statistical analysis

Data were expressed as mean (SD) or number (%) and compared by Student's *t* test or the  $\chi^2$  test. Univariate and multivariate Cox proportional hazards regression models were used to identify independent predictors of late cardiac events. The clinical variables that were entered into the model were sex, age, history of previous myocardial infarction, current smoking, hypertension, hypercholesterolaemia, heart failure, angina pectoris, and the use of  $\beta$  blockers, diuretics, digoxin, calcium antagonists, and angiotensin converting enzyme antagonists. The echocardiographic variables were fixed wall motion abnormalities, reversible wall motion abnormalities, or both, achievement of target heart rate, and typical angina or ST depression during the stress test. Variables were selected in a stepwise forward selection manner with entry and retention set at a significance level of 0.05. The incremental value of DSE over the clinical variables in the prediction of events was assessed by adding various echocardiographic data to clinical and stress test parameters. The risk of a variable was expressed as a hazard ratio (HR) with a corresponding 95% confidence interval (CI). The probability of cardiac event-free survival was calculated by the Kaplan-Meier method and the resulting curves were compared by the log rank test.

## RESULTS

### Clinical and stress test results

Table 1 presents the clinical characteristics of patients. During DSE there was a significant increase in heart rate

(from 74 (14) to 132 (15) beats/min,  $p < 0.001$ ), whereas systolic blood pressure did not change significantly (131 (24) v 129 (24) mm Hg). The mean (SD) maximum dobutamine dose was 37 (8)  $\mu\text{g/kg/min}$ . Atropine was added for 153 (52%) patients. Target heart rate was achieved by 252 (86%) patients. Side effects during DSE were short runs of ventricular tachycardia ( $< 10$  complexes) in 10 (3%) patients, ventricular tachycardia of  $\geq 10$  complexes in three (1%), transient atrial fibrillation in three (1%), and severe hypotension (symptomatic or decrease in systolic blood pressure of  $> 40$  mm Hg) in four (1%). No patient experienced myocardial infarction or life threatening rhythm disorders.

### Echocardiographic data

The test was abnormal (fixed or reversible wall motion abnormalities or both) in 241 (82%) patients. Ischaemia (new or worsening wall motion abnormalities) was detected in 96 (33%) patients. Of these patients, 75 had resting wall motion abnormalities as well.

### Follow up data

Follow up was successful for 331 (99.7%) patients. The decision for late revascularisation was based on the recurrence of symptomatic coronary artery disease or on the occurrence of an acute coronary event (unstable angina, acute myocardial infarction) at least three months apart from the first post-revascularisation DSE.

Thirty eight patients who underwent coronary revascularisation within three months of DSE were excluded from analysis because for these patients the decision to revascularise might have been influenced by test results. Among the remaining 293 patients, 37 (13%) died of any cause and 89 (30%) patients had at least one cardiac event; 21 (7%) patients had a cardiac death, 11 (4%) had a non-fatal myocardial infarction, and 68 (23%) had a late revascularisation.

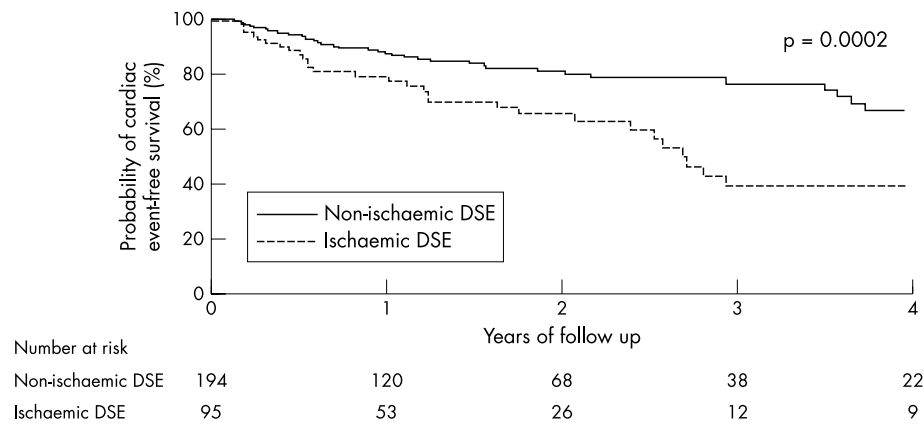
### Predictors of cardiac events

Univariate predictors of the composite of cardiac events were congestive heart failure (HR 2, 95% CI 1 to 3.8), wall motion score index at rest (HR 2.7, 95% CI 1.4 to 5), wall motion score index at peak (HR 2, 95% CI 1.2 to 3.3), reversible wall motion defects (ischaemia) on DSE (HR 2.9, 95% CI 1.7 to 4.8), ST segment depression (HR 2.8, 95% CI 1.2 to 6.3), and angina pectoris (HR 2, 95% CI 1.2 to 3.5) during the test.

**Table 1** Baseline clinical characteristics of 293 patients

Characteristic	Mean (SD) or number (%)
Age (years)	62 (11)
Men	217 (74%)
Hypertension	119 (40%)
Diabetes mellitus	97 (33%)
Smoking	97 (33%)
Hypercholesterolaemia	120 (41%)
Congestive heart failure	46 (16%)
Myocardial infarction	203 (69%)
Coronary angioplasty	174 (59%)
Coronary artery bypass surgery	171 (58%)
1 vessel disease	141 (48%)
2 vessel disease	94 (32%)
3 vessel or left main disease	58 (20%)
Complete revascularisation	202 (69%)
Incomplete revascularisation	91 (31%)
Medication	
$\beta$ Blockers	127 (43%)
ACE inhibitors	128 (44%)
Calcium antagonists	121 (41%)

ACE, angiotensin converting enzyme.



**Figure 1** Kaplan-Meier curves for cardiac events (cardiac death, non-fatal myocardial infarction, late revascularisation) as a function of dobutamine stress echocardiography (DSE) results. Event-free survival differed significantly between patients with and patients without reversible wall motion defects (ischaemia).

Multivariate predictors were hypertension (HR 1.7, 95% CI 1.1 to 2.6), congestive heart failure (HR 2.1, 95% CI 1.3 to 3.2), ischaemia on DSE (HR 2.1, 95% CI 1.3 to 3.2) (fig 1), and ST segment depression on DSE (HR 2, 95% CI 1.1 to 3.8). Among patients with ischaemia on DSE, those who had had a coronary intervention < 2 years before the test had a trend towards more cardiac events compared with patients who had undergone revascularisation > 2 years before ( $p = 0.09$ ) (fig 2). The adverse outcome for patients with ischaemia was equal irrespective of the presence or absence of angina before the test (fig 3).

### Predictors of cardiac death

Univariate predictors of cardiac death were diabetes mellitus (HR 3.6, 95% CI 1.2 to 11.4) and congestive heart failure (HR 6.8, 95% CI 2.8 to 16.3). The same predictors were found after multivariate analysis (HR 4.9, 95% CI 1.4 to 17.3 for diabetes mellitus and HR 10.5, 95% CI 3.8 to 29.3 for congestive heart failure).

### Predictors of hard events

The only predictor of hard events (cardiac death plus myocardial infarction) was congestive heart failure (HR 4.7, 95% CI 2.3 to 9.6 in univariate analysis and HR 8.1, 95% CI 3.5 to 18.5 in multivariate analysis).

## DISCUSSION

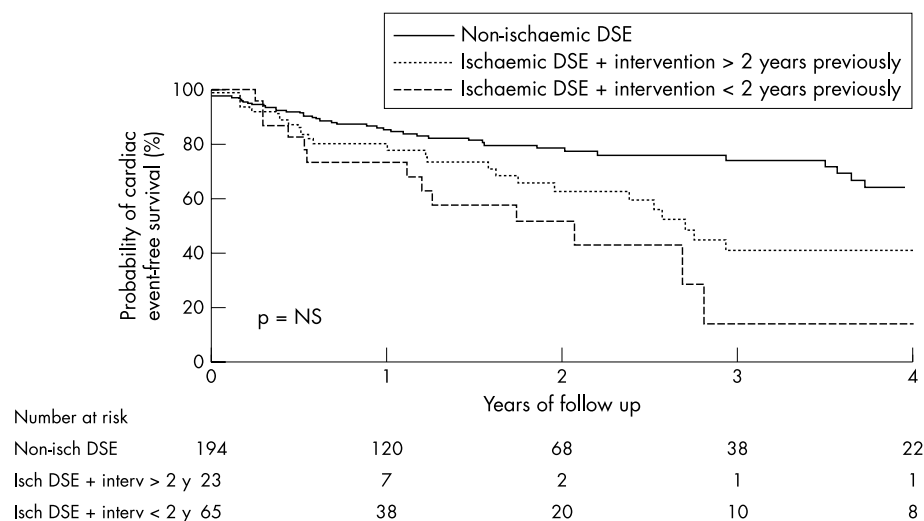
We assessed the independent value of DSE for prediction of cardiac events in 331 patients with previous revascularisation.

During a mean period of 24 (20) months, 89 patients had at least one late cardiac event. The presence of congestive heart failure predicted cardiac death or myocardial infarction, whereas diabetes mellitus was an independent predictor of cardiac death. Clinical predictors of cardiac events were hypertension and congestive heart failure. Ischaemia on DSE, indicated by either reversible wall motion abnormalities or ST segment depression, was associated with increased risk of cardiac events after controlling for clinical parameters. According to the classic ischaemic cascade, ST segment changes follow perfusion and wall motion abnormalities on imaging stress testing. However, Picano<sup>9</sup> has proposed an alternative ischaemic cascade when endothelial dysfunction and impaired coronary flow reserve are present without significant epicardial coronary artery lesions. According to this model, ST segment changes come first, perfusion abnormalities come second, and echocardiographic changes are usually absent in the case of milder, "patchy" degrees of myocardial ischaemia. Hence, coronary endothelial dysfunction and impaired flow reserve are likely to have an adverse effect on prognosis after coronary revascularisation.

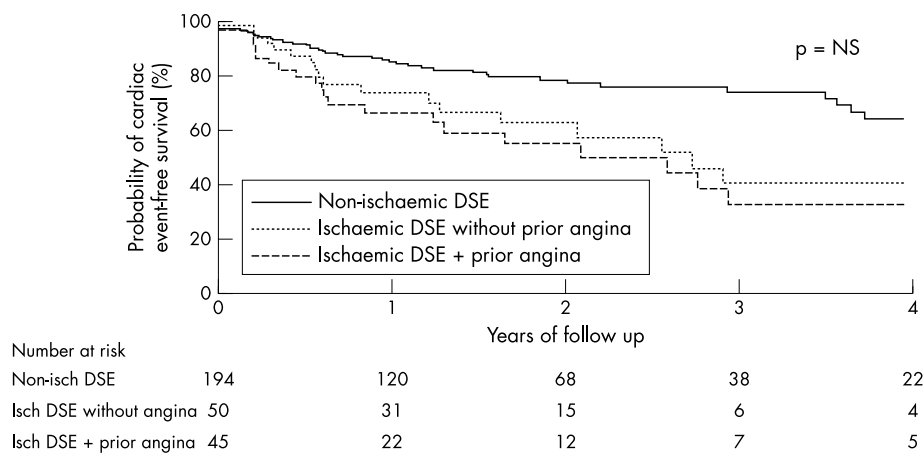
The risk associated with myocardial ischaemia was observed among patients who had their revascularisation performed within two years, as well as among patients who had been revascularised > 2 years before DSE.

### Impact of symptoms on outcome

Restenosis is the major limitation of coronary interventions. It occurs usually within several months after a successful



**Figure 2** Kaplan-Meier curves for cardiac events (cardiac death, non-fatal myocardial infarction, late revascularisation) as a function of DSE results. Among patients with reversible wall motion defects (ischaemia) event-free survival did not differ significantly between patients who were revascularised > 2 years and patients who were revascularised < 2 years before the test. NS, not significant.



**Figure 3** Kaplan-Meier curves for cardiac events (cardiac death, non-fatal myocardial infarction, late revascularisation) as a function of DSE results. Among patients with reversible wall motion defects (ischaemia) event-free survival did not differ significantly between patients with and patients without a history of angina pectoris.

percutaneous coronary intervention, with an incidence as high as 33% in some patient subsets.<sup>10</sup> After coronary bypass surgery, the atherosclerotic process increases over the years, leading to vein graft patency of < 65% 10 years after surgery.<sup>11</sup> According to the guidelines of the American College of Cardiology/American Heart Association, stress testing is recommended after coronary revascularisation only for patients with recurrent symptoms that suggest ischaemia (class I) or as part of cardiac rehabilitation (class IIa).<sup>12</sup> However, symptoms after revascularisation are commonly atypical and they cannot be considered to be reliable determinants of restenosis or graft occlusion. The usefulness of non-invasive imaging for asymptomatic patients after coronary revascularisation has been questioned in previous studies. Lauer and colleagues<sup>13</sup> studied 873 symptom-free patients after coronary artery bypass grafting by exercise thallium-201 and found that thallium perfusion defects and impaired exercise capacity were strong and independent predictors of death or non-fatal myocardial infarction. Sarda and colleagues<sup>14</sup> found an independent predictive value of <sup>201</sup>Tl myocardial scintigraphy after coronary artery bypass grafting in a patient population consisting mainly of patients who were asymptomatic before the test. In the present study, the presence of angina pectoris before the test was not associated with more cardiac events among patients with reversible wall motion abnormalities on DSE. Consequently, physicians cannot rely on symptoms after revascularisation to determine the risk for future cardiac events. Evidence of reversible wall motion abnormalities during dobutamine stress predicts which patients are at a high risk of developing late cardiac events, even if they are asymptomatic after a coronary intervention. A more aggressive treatment may be justified for these patients.

### Comparison with previous studies

Authors of a large number of studies have reported on the incremental prognostic value of DSE in the general population,<sup>1 2 4-6</sup> as well as in particular patient subsets.<sup>15-20</sup> To our knowledge, this is the first study to assess the prognostic value of DSE for patients with prior coronary revascularisation. However, exercise echocardiography has been found to predict cardiac events among patients after coronary artery bypass surgery.<sup>21</sup> In addition, several studies have reported the prognostic value of nuclear scans for previously revascularised patients. Palmas and colleagues<sup>22</sup> found an incremental prognostic value of <sup>201</sup>Tl for 294 patients ≥ 5 years after coronary artery bypass graft surgery. Miller and associates<sup>23</sup> reported a similar prognostic value for <sup>201</sup>Tl within two years after surgical revascularisation. In other studies,<sup>201</sup>Tl was predictive of cardiac events for patients 1-3

years after coronary angioplasty<sup>24</sup> and for patients early (5 (2) months) after coronary stenting.<sup>25</sup> The present findings indicate that DSE can alternatively be used as a prognostic tool for these patients.

### Study limitations

Readers of DSE results were not blinded to clinical information and data concerning previous revascularisations. Additionally, physicians were free to modify treatment according to DSE results. Thus, administration of medication that has been proved to reduce cardiac events and improve outcome, such as β blockers and angiotensin converting enzyme inhibitors, might have influenced patient prognosis. Finally, our results were obtained in a single centre with a high volume and experience with DSE; hence, our results do not necessarily apply to other, less experienced centres.

### Conclusions

DSE provides incremental data to the clinical information on the prognosis of patients after revascularisation. Evidence of myocardial ischaemia, based on reversible wall motion abnormalities during dobutamine infusion, is an independent predictor of cardiac events.

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## IMAGES IN CARDIOLOGY

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### Aortic arch aneurysm

A 68 year old man was admitted to hospital for an ischaemic stroke. His medical history revealed hypertension, diabetes mellitus, chronic atrial fibrillation, and a blunt trauma sustained during a motor vehicle accident. Routine chest x ray revealed an enlarged superior mediastinal silhouette (left panel). Subsequently, magnetic resonance imaging (MRI) showed a thoracic saccular aneurysm of the aortic arch with involvement of the branches (right panel).

Transverse arch aneurysms are relatively uncommon, comprising only 11% of all aortic aneurysms. Saccular thoracic aneurysms are frequently post-traumatic (high speed deceleration accidents); other causes include syphilis, autoimmune disorders, and atherosclerosis. The most frequently involved location is the relatively immobile isthmus just distal to the origin of the left subclavian artery, adjacent to the attachment of the ligamentum arteriosus.

Many thoracic aneurysms are visible on chest x ray and are characterised by widening of the mediastinal silhouette, enlargement of the aortic knob or



displacement of the trachea of the mid-line.

However, saccular aneurysms may not be evident on the chest x ray.

MRI is useful in detecting aneurysms and especially magnetic resonance angiography may prove to be useful in defining the anatomy of aortic branch vessels. The aneurysm in this patient may be caused by atherosclerotic disease and/or his deceleration trauma.



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